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Statement of Purpose:

AIDS Treatment News reports on experimental and standard treatments, especially those available now. We interview physicians, scientists, other health professionals, and persons with AIDS or HIV; we also collect information from meetings and conferences, medical journals, and computer databases. Long-term survivors have usually tried many different treatments, and found combinations that work for them. *AIDS Treatment News* does not recommend particular therapies, but seeks to increase the options available.

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Antiretroviral Pipeline: New-Drug Reports from Retroviruses Conference

by John S. James

Here are short summaries on the three experimental antiretrovirals that were most discussed at the 11th Conference on Retroviruses and Opportunistic Infections, February 8-11, 2004 in San Francisco. They received attention because they reported significant data from human HIV trials, and because they were highlighted in the conference program and press materials.

Other antiretrovirals presented at the conference were at least as interesting, but at an earlier stage of development.

We expect to report later on many of the following: PA-457, SPD-754, GW873140, GW678248, SN1212/1461, TMC114, TNX-355, PRO140, UK-427,857, AK602, KRH-2731, mifepristone (RU-486), and chloroquine.

BMS-488043: New Mechanism to Stop HIV Entry

This new compound from Bristol-Myers Squibb works differently from any approved drug; therefore, cross-resistance with existing drugs would not be expected. BM-488043 prevents the first step of infection, by attaching to the gp120 protein on the virus and blocking its attachment to the CD4 receptor on the cell.(1-3)

Note that the approved drug T-20 (Fuzeon) blocks viral fusion with the cell at a later step in the attachment process; since the two drugs work at different steps of HIV entry into cells, cross-resistance is unlikely. Also, BMS-488043 is a small-molecule drug candidate, so it will be much less expensive to manufacture than T-20. It can be given orally, and can reach blood concentrations in healthy human volunteers about 10 times greater than what is expected to be needed to block HIV replication.

Shortly before the conference the company received "proof of principle" that the drug can reduce HIV in people: data showing that the compound did lower viral load and appeared to be safe, in an 8-day trial in 30 HIV-positive volunteers.

Reverset: Nucleoside Analog Active Against Resistant Viruses

Reverset is a nucleoside analog (in the same class as AZT, 3TC, abacavir, tenofovir, and others), but is active against most of the viruses resistant to the approved antiretrovirals, as well as against wild-type, non-resistant virus. A small (30-volunteer, 10-day) trial reported at the Retroviruses conference found that the drug appeared to be safe, and caused an average 1.7 log (98%) drop in HIV viral load.(4) Reverset can be taken once a day, and laboratory tests did not find evidence of mitochondrial toxicity, believed to cause the neuropathy and other side effects of some antiretrovirals.

Reverset was invented at Emory University and developed by Pharmasset (http://www.pharmasset.com/), which recently entered into a licensing agreement with Incyte Corporation (http://www.incyte.com/) to co-develop Reverset. Before the recently completed trial, it had been tested for safety in 56 HIV-positive volunteers.

Schering D: Targeting CCR5 Virus

After HIV attaches to the CD4 receptor on a human cell, it must then attach to a co-receptor -- usually either CCR5 or CXCR4. Almost always the virus that first infects a person uses CCR5; later, CXCR4 virus will evolve in some but not all patients. Different drugs are now being developed to target viral attachment to each of these co-receptors.

Schering D (SCH D), which blocks attachment to the CCR5 co-receptor, is

an improvement over Schering C. It is active against HIV at about one tenth the concentration needed of Schering C, and appears to be safe in trials so far.

At the Retroviruses conference, results were reported from a trial of 48 patients treated for 14 days with one of three different doses of Schering D, or with a placebo. Viral load reductions were about one log at the lowest dose tested, 1.6 logs at the highest dose.(5)

References

Note: Unless otherwise stated, all references refer to the 11th Conference on Retroviruses and Opportunistic Infections, February 8-11, 2004, in San Francisco. You can see these abstracts at the official conference site:
http://www.retroconference.org/2004/home.htm
(click on 'Search Abstracts'). You may want to find the abstract by searching in the Abstract Title field for an important word. Another way is to search in the Presentation Number field for the abstract number. In case the search only shows a few lines of the result, try a different Web browser.

1. G Hanna, J Lalezari, J Hellinger and others. Antiviral activity, safety, and tolerability of a novel, oral small-molecule HIV-1 attachment inhibitor, BMS-488043, in HIV-1-infected subjects. 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, February 8-11, 2004 [abstract 141]

2. PF Lin, HT Ho, YF Gong, and others. Characterization of a small molecule HIV-1 attachment inhibitor BMS-488043: virology, resistance and mechanism of action. [abstract 534]

3. G Hanna, J-H Yan, W Fiske, T Masterson, D Zhang, and D Grasela. Safety, tolerability, and pharmacokinetics of a novel, small-molecule HIV-1 attachment inhibitor, BMS-488043, after single and multiple oral doses in healthy subjects. [abstract 535]

4. RL Murphy, D Schurmann, A Beard, L Cartee, RF Schinazi, and MJ Otto. Tolerance and potent anti-HIV-1 activity of Reverset following 10 days of mono-therapy in treatment-naive individuals. [abstract 137]

5. D Schurmann, R Rouzier, R Nougarede, and others. SCH D: Antiviral activity of a CCR5 receptor antagonist. [abstract 140LB]

FDA Advisory Hearing on New-Fill (Sculptra), March 25, 2004 in Gaithersburg, Maryland

On March 25, 2004 the FDA's General and Plastic Surgery Devices Panel will hold a public hearing on "a premarket approval application (PMA) for an injectable device intended for use in the correction of lipoatrophy of the face in HIV (human immunodeficiency virus) positive patients." *AIDS Treatment News* has learned that the application is for Sculptra, which is marketed in Europe under the name New-Fill. According to the Web site Drugs.com, it has been used by an estimated 100,000 people worldwide for various facial treatments.

Those who want to speak at the hearing should notify the FDA before March 15.

For more information on the logistics, visit:
http://www.fda.gov/cdrh/panel/index.html
Click on "Upcoming CDRH Advisory Committee/Panel Meetings" then on "Details" for the March 25, 2004 meeting.

Also, background information on this application will be available to the public

one day before the meeting, at: http://www.fda.gov/cdrh/panelmtg.html

Lipodystrophy: Conference on Imaging Technologies in Clinical Management, Montreal, April 2-3, 2004

A conference on "Clinical Applications of Imaging Technologies in the Management of the HIV Lipodystrophy Syndromes" will be held April 2-3, 2004 in Montreal. Speakers include Andrew Carr, Carl Grunfeld, Donald Kotler, Kathy Mulligan, Pablo Tebas, more than ten other physicians, and Bob Munk of New Mexico AIDS InfoNet on financial considerations.

For more information see the conference Web site: http://www.cmccanada.ca

Micronutrient Supplementation Shows Promise in Placebo-Controlled Trial

by John S. James

A small (40-patient) randomized trial in patients on HAART with peripheral neuropathy showed a statistically significant increase in CD4 (T-cell) counts over 12 weeks.(1) Neuropathy, the primary focus of this trial, also decreased -- but it decreased almost as much in the placebo group, so the difference was not statistically significant. Viral load also decreased, but again not to a statistically significant degree. The possibility of nutritional treatment to reduce neuropathy deserves further investigation, however, because statistical proof could easily have been missed in this small trial.

This study was designed by Jon D. Kaiser, M.D., and others. Dr. Kaiser, the author or Healing HIV: How to Rebuild Your Immune System (HealthFirst Press, 1999), is well known for combining mainstream HIV treatment with nutritional supplements, acupuncture, and other complementary approaches. All the volunteers in this trial were on stable HAART regimens that included d4T and/or ddI, drugs that can cause neuropathy. HIV infection itself can also cause neuropathy.

The nutritional supplement was formulated based on Dr. Kaiser's HIV treatment experience, and contains 33 vitamins, minerals, and antioxidants. The list was published on the poster at the Retroviruses conference, and is available online.(2) The supplement itself is also available through the Web site (the "high-dose" formulation is the one used in this trial). Of note, there were no gastrointestinal side effects reported during the trial.

Due to the luck of the draw in the randomization for this small trial, the volunteers in the micronutrient group had a lower baseline CD4 count (356 vs. 467) and a longer duration of neuropathy (21.4 months vs. 12.2). In addition, three in the micronutrient group had diabetes. (3) Some trial designs randomize among matched pairs to prevent this kind of

accidental bias, but that was not done in this case. These differences (all to the detriment of the micronutrient group), plus the small size of the trial and the difficulty of treating long-standing neuropathy, made it unlikely that this trial could show a statistically significant neuropathy improvement, even if a benefit did exist.

The trial was conducted at four U.S. research sites -- one of them Philadelphia FIGHT, where *AIDS Treatment News* is located. During the trial we heard from staff that patients seemed to be doing well. The trial was blinded at the time, and no one knew who was getting the placebo.

This is one of the few nutritional studies that has been presented at the Retroviruses conference, which is heavily oriented toward basic science.

Note: A much less expensive formula of 21 micronutrients was shown to reduce death in a trial in Thailand, among volunteers with a CD4 count less than 200 who were unable to obtain HAART. (4) Its cost in Thailand was about U.S. $1.00 per month.

References

(1) J Kaiser, J Ondercin, G Santos, G Leoung, S Brown, M Mass, and M Baum. Broad-spectrum micronutrient supplementation in HIV-infected patients with dideoxynucleoside-related peripheral neuropathy: A prospective, double-blind, placebo controlled trial. 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, February 8-11, 2004 [abstract 494].

(2) http://www.integrativehealthconsulting.com

(3) Personal communication from Dr. Kaiser.

(4) S Jiamton, J Pepin, R Suttent, and others. A randomized trial of the impact of multiple micronutrient supplementation on mortality among HIV-infected individuals living in Bangkok. *AIDS.* Volume 17, pages 2461-2469, 2003. The formula (which may less applicable to other regions because of differences in prevailing nutrition and deficiencies) is available online at: http://www.aidsmap.com/news/newsdisplay2.asp?newsId=2412
Note that all the doses are listed by weight -- not always the numbers U.S. readers are familiar with.

Nevirapine Precautions Published

Physicians starting patients on nevirapine (Viramune[R]) need to be aware of new precautions published in February 2004 by Boehringer Ingelheim. A nevirapine combination is recommended as an "alternative" antiretroviral starting regimen in the current U.S. treatment guidelines,(1) but may be the best starting regimen for some patients -- for example, because of its favorable effect in raising HDL ("good cholesterol"). The new warning is paradoxically good news, because it helps avoid problems with nevirapine, including identifying which patients should use it very cautiously or not at all. For example, women with a CD4+ count *above* 250 have a 12 times greater risk of liver toxicity than other patients. And patients need special monitoring when they start nevirapine treatment, because the risk of problems is greatest then.

For more information see the following at http://www.viramune.com/

* The "Dear Health Care Professional" letter from Boehringer Ingelheim;

* The new "black box" warning in the Viramune prescribing information; and

* "Guidelines for the Management of

Rash with Viramune," and "Guidelines for the Management of Hepatitic Events with Viramune."

References

1. http://www.aidsinfo.nih.gov/guidelines/

Prison HIV and Hepatitis C Sites

Of the hundreds of good Web sites on HIV, hepatitis C, and prison issues, *AIDS Treatment News* has chosen about 40 to help you get started in finding the information or resources you need. Annotated links are at:
http://www.aidsnews.org/prison/

"Poppers," Some Other Drugs, May Increase HIV Infection Risk

by John S. James

Users of amphetamines ("crystal"), hallucinogens, or inhaled nitrites ("poppers") had higher rates of HIV infection than non-users,(1) in an analysis of the Vaxgen trial data presented at the 11th Conference on Retroviruses and Opportunistic Infections, February 8-11, 2004.

This information was collected from 4,697 high-risk HIV-negative men who have sex with men, who were enrolled at 56 clinical-trial sites in the U.S. for the 36-month trial. Overall, there were 2.8 HIV infections per 100 person-years -- already considered a high number. But amphetamine users had 4.5 infections per 100 person-years, hallucinogen users had 4.0, and poppers users had 3.6. In this high-risk cohort there were many more users of poppers than of the other two put together -- 2176 reported poppers use, vs. 901 amphetamines and 603 hallucinogens -- suggesting a potentially large impact on the spread of HIV.

The drugs may be having this effect by making people more likely to take risks they would otherwise have avoided. Some drugs might also affect the immune system directly. In August 1999 *AIDS Treatment News* noted animal studies showing that exposure to "poppers" increased cancer growth(2) and bacterial growth(3), probably by suppressing the animals' natural immunity.

Comment

The higher rates of HIV infection found could also be due to selection bias -- if, for example, those who accept the risks of using illegal drugs also tend to take more risks in other areas, such as unprotected sex. The difference in this case is that the drugs would not be contributing to increased infection, but only identifying those already at higher risk. Both mechanisms could be involved, with drug both contributing to infection and also indicating who was already more likely to be infected.

References

(1) M Ackers, A Greenberg, C Lin and others. High HIV incidence among men who have sex with men participating in an HIV vaccine efficacy trials, United States, 1998-2002. 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, February 8-11, 2004. [abstract 857]

(2) Soderberg LSF. Increased tumor growth in mice exposed to inhaled isobutyl nitrite. *Toxicology Letters* , 1999; volume 104, pages 35-41.

(3) Schafer R, Barnett J, Soderberg L, and Damiani C. Pulmonary exposure to isobutyl nitrite reduces resistance to a respiratory infection. 10th International Congress of Mucosal Immunology, Amsterdam, June 27 to July 1, 1999.

New Testing for Very Early HIV Diagnosis

The commonly used HIV antibody test does not catch a very recent HIV infection, because it takes a few weeks for the body to create enough antibodies to show in the test. Other tests can detect the virus directly, but because they are expensive and pick up relatively few cases, they have not been routinely used in HIV testing. Now there is a public-health push to get the earlier results. This is because persons who are newly infected but have not developed antibodies yet are likely to have extremely high viral loads, and therefore have a high risk of transmitting the infection to others; a significant fraction of new infections may be transmitted this way. And when public-health experts can see immediately where new infections are headed, they can target prevention campaigns more effectively. Also, patients can get medical care for the early ("primary") HIV infection.

A report from North Carolina, where the state's 110 public HIV testing sites have offered the enhanced HIV testing since November 2002, provided the following information.(1) Of 109,788 persons tested, 622 were found to be HIV infected; of these, 21 were negative on the regular antibody test but found to be infected by directly testing for the virus. Nineteen of them (including one pregnant woman) began medical care and were offered antiretroviral treatment. And the testing program gave the first evidence of an epidemic of HIV infection among college men, mostly African Americans, at least in North Carolina, where the information was collected(2) -- allowing better targeting of prevention efforts.

A different approach to testing for recent HIV infection is STARHS (Serologic Testing Algorithm for Recent HIV Seroconversion). In STARHS, persons who have tested positive with the usual antibody test have a portion of their serum saved for a second antibody test, deliberately made less sensitive (it is sometimes called the "detuned assay"). Those who were infected recently, within about the last year, may not have enough antibodies yet to test positive on the detuned test, even though they tested positive on the regular HIV test. Note that STARHS only applies to persons who have tested positive with the regular HIV test -- not those picked up only by a direct test for the virus, whose serum would certainly show up negative on the detuned test used for STARHS.

Notes:

* STARHS testing is not very reliable for an individual -- but more accurate for a population, since it wrongly classifies about the same number of people as early or late infection.

* STARHS is needed in addition to the direct viral test, because it picks up many more new infections, helping epidemiologists better understand where the epidemic is moving now.

* The public-health use of STARHS was delayed when Abbott Laboratories withdrew its test from the market. Now another detuned test is available.

References

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2. LB Hightow, P MacDonald, CD Pilcher and others. Transmission on campus: Insights from tracking HIV incidence in North Carolina. 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, February 8-11, 2004 [abstract 84].